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EXAMINER	
TURNER, SHARON L	
ART UNIT	PAPER NUMBER
1647	

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19

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/739,933	REID ET AL.	
	Examiner	Art Unit	
	Sharon L. Turner	1647	

-- Th MAILING DATE of this communication app ars on the cover sheet with th correspond nce address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 January 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26 and 28-64* is/are pending in the application.

4a) Of the above claim(s) *9-15,17-19,21-26,28-32 and 34-62* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,16,20,33,63 and 64* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) *1-26 and 28-64* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *18* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Response to Amendment

1. The amendment and declaration filed 1-6-03 have been entered into the record and have been fully considered.

2. The text of Title 35 of the U.S. Code not reiterated herein can be found in the previous office action.

3. As a result of Applicant's amendment, all rejections not reiterated herein have been withdrawn by the Examiner.

4. Claim 27 is canceled. Claims 1-26 and 28-64 are pending.

Election/Restriction

5. Applicant's election with traverse of Group I, claims 1-8, 16, 20, 27 and 33 in part to the extent drawn to TGF-ALPHA-α, second compound that inhibits a naturally occurring signal that inhibits migration and neurodegenerative disease, in Paper No. 13 is acknowledged. The traversal is on the ground(s) that the search and examination of the different inventions and species would not be burdensome or unreasonable. This is not found persuasive because the methods are distinct as they are comprised of different steps, utilize different reagents and achieve distinct results as claimed. Thus, a search for one of the methods or species would not be co-extensive with a search for any other method or species.

The requirement is still deemed proper and is therefore made FINAL.

6. Claims 9-15, 17-19, 21-26, 28-32 and 34-62 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention or species, there being no allowable generic or linking claim. Applicant timely traversed the

restriction (election) requirement in Paper No. 13. It is noted that withdrawn claims 9-15, 21-26, and 28-32 are drawn to divergent species not clearly directed to the elected subject matter. These claims differ from applicant's statement of claims readable on the invention.

7. This application contains claims 9-15, 17-19, 21-26, 28-32 and 34-62 drawn to an invention nonelected with traverse in Paper No. 13. A complete reply to the final rejection must include cancelation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:
> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1-8, 16, 20 and 33 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claims 1, 20 and 33 are amended to newly recite "wherein said administration is outside of the ventricles." Applicants point to support in the specification for the new recitation at p. 12, lines 20-25 and Example 3. However, the specification at such places does not support the

limitation. Thus, the recitation appears to be new matter absent evidentiary support as filed.

10. Claims 1-8, 20 and 33 stand rejected under 35 U.S.C. 112, first paragraph as set forth in Paper No. 14 (8-5-02), as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The claims recite contacting with a compound that binds to an epidermal growth factor (EGF)/ErbB family receptor, which attracts glial progenitor cells or progeny thereof and which stimulates differentiation of the glial progenitor cell or progeny thereof. Claim 27 recites a second compound that is capable of inhibiting a naturally occurring signal that would otherwise inhibit migration of the glial progenitor cell or its progeny. While the disclosure teaches that Transforming growth factor alpha is a molecule which binds EGF receptor, the recitation of alternatively described molecules which merely maintain such functional activities as noted above represents a functional recitation of multiple distinct classes of molecules which are not structurally described but which are encompassed by the claims. While the disclosure provides written description of TGF-ALPHA, the disclosure fails to provide a written description supportive of all means of achieving such function, but only those in possession by applicant at the time of the invention, see MPEP 2164.08(a). Thus, the written description provided by the disclosure is not commensurate with that claimed and the artisan cannot conceive based on the single species the genus of molecules claimed. Moreover, there appears to be no single embodiment disclosed for the recitation of the second compound in claim 27.

A genus claim may be supported by a representative number of species as set forth in Regents of the University of California v Eli Lilly & Co, 119F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997), which states:

"To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention". Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1980) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed.") Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d 1565, 1572, 41 USPQ2d at 1966.

An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. Fiers v. Revel, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id at 1170, 25 USPQ2d at 1606."

Here, the description for the first compound provides only a single species and no description of the structural requirements of the molecules, falling within the scope of the genus, or of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus. However, it is noted that no single species is recognized for the second compound as noted in claim 27. The artisan readily recognizes the unpredictability in the art in determining structure function relationships

of peptides and peptide families even amongst highly conserved variants, see in particular Skolnick et al., Trends in Biotech., 18(1):34-39, 2000. Given the unpredictability of homology comparisons, and the fact that the specification fails to provide objective evidence any additional peptide sequences that are indeed species of the claimed genus', it cannot be established that a representative number of species have been disclosed to support the genus' molecules claim. Thus, instant claims lack adequate written description support for the first and second compounds of the claims.

Applicants argue that the specification provides a description of compounds that were known to bind and activate an EGF-R, see specification at p. 12, line 28 and that the structure of such compounds were known to the artisan at filing. Applicants point out that a number of these ligands share structural features, for example as depicted in Exhibit 2. Applicants note Example 3. Applicants argue that based on such disclosure those in the art would have reasonably expected that other EGF-R binding compounds would also function to attract a glial progenitor cell as claimed.

Applicant's arguments filed 1-6-03 have been fully considered but are not persuasive. Applicant's arguments suggest that the artisan would have known the structure of those alternative compounds encompassed by the claim but for which no EGF-R binding is known. The claim is directed to a generic recitation of all compounds capable of binding. Yet the artisan is not directed to any particular structure that should be conserved in order to achieve such effect. While particular EGF-R binding compounds are known as disclosed at p. 12, line 28, the claims are not directed to such structures, or to any particular or similar structure that when conserved achieves such binding. The claims are directed to an unlimited diversity of molecules that cannot be predicted and for which the artisan is not provided any guidance either via the specification or the general skill in the art by which to determine suitable binding

structues. Thus, the claims as directed to a functional recitation in the absence of any structure is insufficient to exhibit to the artisan that applicant was in possession of the invention now claimed.

11. Claims 1-8, 20 and 33 stand rejected as set forth in Paper No. 14 (8-5-02) under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for TGF-α binding to the EGF receptor, does not reasonably provide enablement for the generic recitation of all compounds which bind to the EGF receptor to attract a glial progenitor cell or progeny thereof or to stimulate differentiation as claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specifications disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without undue experimentation. The factors relevant to this discussion include the quantity of experimentation necessary, the lack of working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims.

The claims are akin to a single means claim, i.e., where a means recitation does not appear in combination with another recited element of means. In the instant case the claim does recite an element of means. However, the element of means is described only as a compound that binds the EGF/erbB family receptor. While the specification teaches that TGF-ALPHA is such a polypeptide, the disclosure falls short of describing any other structural molecules that bind EGF receptor to produce the noted effects. Thus, it seems that the claim is subject to an undue breadth rejection under 35 USC 112, first paragraph. In particular MPEP 2164.08(a) and In re Hyatt, 708F.2d 712, 714, 715 (218 USPQ 195, 197) (Fed. Cir. 1983) describe where a single

means claim which covered every conceivable means for achieving the stated purpose was held non-enabling for the scope of the claim because the specification disclosed at most only those means known to the inventor. When claims depend on a recited property, a fact situation comparable to Hyatt is possible, where the claim covers every conceivable structure (means) for achieving the stated property (result) while the specification discloses at most only those known to the inventor.

It is further noted that applicant's disclosure fails to teach the structural and functional relationship recited, i.e., the compound(s) able to produce the required attraction of glial progenitor cells or progeny thereof and to stimulate differentiation of glial progenitor cells or progeny thereof as claimed. Moreover, there is no single embodiment recognized for the second compound as claimed in claim 27. No molecule with the noted properties is disclosed. In particular as noted by Kudlow et al., J. Biol Chem 259(19):11895-900, 1984 and Carpenter et al., PNAS 80(18):5627-30, 1983 binding of the EGF receptor fails to ensure that normal effects are produced as exemplified by two EGF receptor antibodies which bind but fail to activate receptor properties in different systems. The skilled artisan thus would have reason to doubt that merely binding the receptor is sufficient to produce the claimed effects in neural progenitor cells.

Moreover as directed to functional fragments of TGF-ALPHA, the specification fails to teach the required structural identity of such molecules that are capable of not only attracting progenitor cells but producing differentiation. There is no guidance as to which portions of the molecule are required to be retained to maintain the functional activity. The skilled artisan readily recognizes the unpredictability in the art of determining structure function relationships even amongst highly homologous family

members, see in particular Skolnick et al., Trends in Biotech., 18(1):34-39, 2000, Abstract and Box 2.

Thus, for the aforementioned reasons the skilled artisan would not be able make and use the claimed invention, commensurate in scope with the claims, without further undue experimentation to discover those molecules of first and second compounds capable of producing the claimed effects.

Applicants argue that the specification describes methods for attracting a glial progenitor cell or progeny thereof to a site of CNS damage or lesion via a working example using TGF-alpha. Applicants argue that the specification further provides description of how to determine whether a compound binds and attracts such cells, p. 29, lines 7-24 and example 3. Applicants argue that each and every compound need not be exemplified, that the claims require that the glial progenitor cell or its progeny be attracted to a site of CNS damage or lesion and that the claims exclude compounds that do not work. Applicants argue that based on such disclosure the artisan would reasonably expect that other compounds that bind EGF-R would also attract glial progenitor cells as claimed.

Applicant's arguments filed 1-6-03 have been fully considered but are not persuasive. Applicant's exemplification is limited to a single member, TGF-alpha. While the artisan may be adept at testing for molecules that bind EGF-receptor molecules the specification does not provide data to conclude that binding alone is predictable or sufficient to stimulate attraction of glial progenitor cells as claimed. The argument presumes that the single molecule is predictive of the larger family of molecules. However, as evidenced by Beerli et al., J. of Biol. Chem., 271(11):6071-6076, 3-15-1996, EGF related peptides activate distinct subsets of ErbB receptors and differ in their biological activities. Thus, the ability to test molecules for binding to EGF

is not a suitable assay to predict the molecule's function in vivo in attracting glial progenitor cells as claimed. For example, it is noted that the art does not apparently recognize betacellulin as a glial progenitor cell migratory molecule. Even as of August 2000 betacellulin, does not appear to be capable of stimulating migration of glial progenitor cells or of glial progeny. As disclosed in Dunbar et al., Intn'l J. of Biochem. & Cell Biol., 32(8):805-815, 2000, betacellulin is thought to play a role in the differentiation of pancreatic beta cells and the role of betacellulin in vivo is not known. At this juncture, there is no evidence by which to conclude that binding alone is sufficient to provide for glial progenitor cell migration and the specification does not exemplify the use of such assay to predict such effects, particularly in vivo. The standard of an enabling disclosure is one of the ability to make and use, not to make and test to see if any particular molecule will work. Thus, given the unpredictability in the art of determining a proteins function based solely on it structure, see in particular Skolnick et al., of record, and the inability to predict ligand/receptor interaction and function in glial progenitor cell migration based on binding assays, the artisan would be forced to perform further undue experimentation to determine which molecules were capable of binding and further which molecules were capable of producing the claimed effects.

Claim Rejections - 35 USC § 102

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (e) the invention was described in-
>
> (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an

international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application published under section 122(b) only if the international application designating the United States was published under Article 21(2)(a) of such treaty in the English language; or

(2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).

13. Claims 1-8, 16 and 33 stand rejected and claims 20, 63-64 are rejected under 35 U.S.C. 102(e) as being anticipated by Weiss et al., 5,980,885, filed June 7, 1995 and issued Nov. 9, 1999.

It is disclosed as is recognized in the art that TGF-ALPHA binds the EGF receptor, see in particular p. 2 and Todaro et al., PNAS 77:5258-62, 1980.

Weiss et al., teach administration of TGF-ALPHA to brain for the purpose of inducing in vivo proliferation, migration and differentiation of neural and/or glial cells and for treatment of Huntington's, Alzheimer's, Parkinson's and other neurological disorders, see in particular Abstract, column 26, lines 16-26 and Examples 27-30. In addition, the method may be used in areas of demyelination or autoimmune disease such as MS for proliferation of glial schwann, see in particular columns 24-25. The method is also disclosed for use in the replacement of neurons, for example as transplants or grafts, disclosed at column 23. Weiss further teaches that the method may be generically used to replace damaged or missing neurons and/or glia, see in particular Abstract.

As the treatment of Weiss involves administration of TGF-ALPHA to the brain and results in the contact of TGF-ALPHA, a compound that binds the EGF receptor with neural progenitor cells within the brain, the treatment taught by Weiss is necessarily the same as that claimed because the treatment comprises the same reagents, steps and effects as noted. Thus, the reference teachings anticipate the claimed invention.

Applicant's argue that Weiss only show intraventricular injection of growth factors to animals that have no CNS damage or lesion, that the administration to ventricles does not function to induce migration of glial progenitor cells toward a site of CNS damage or lesion and that the claims thus teach over the invention.

Applicant's arguments filed 1-6-03 have been fully considered but are not persuasive. In particular Weiss teaches injection of growth factors to animals having CNS damages or lesion, see in particular column 22, lines 10-17. Weiss further teaches administration at sites other than in the ventricle, but that are within the CNS, see in particular column 23, lines 4-21. It is however noted that the striatum is adjacent the ventricles and is accessible thereby as disclosed in Weiss, see in particular column 26, 41-45.

New claim 1 is amended to recite that the method is for attraction to a site of damage or lesion. New claims 1 and 33 are amended to recite that the compound is administered outside of the ventricles wherein the glial progenitor cell or progeny thereof is attracted to the site of damage or lesion in the CNS tissue. Weiss et al., teach that the administration of the growth factors can be done by any method, including injection cannula, transfection of cells with growth hormone-expressing vectors, injection, and timed release apparati which can administer substances at the desired site, see in particular column 25, lines40-column 26, line 15. Such sites include transplantation to basal gangia, caudate, putamen, nucleus basalis or substantia nigra, i.e., into the striatum as claimed, see in particular column 23, lines 4-21. Also the compositions may be administered via oral administrations, see in particular column 25, lines 40-55. Additionally it is noted that dopamine cells can be generated in the striatum by the administration of a composition comprising growth factors to the lateral ventricle and that for treatment of MS or other deyelinating diseases growth factors

would be delivered to the central canal, see in particular column 26, lines 39-55. Thus the administration of the growth factors may be inside or outside of the ventricles. Moreover, Weiss contemplates administration at the site of damage or lesion where promotion of growth, differentiation and migration of neural and glial cells would occur. For example, In columns 60 Weiss teaches a Huntington's and Parkinson's Disease model wherein transplants are injected into the substantial nigra at the site of lesion as described in Examples 1-5 and 27.

New claim 20 recites wherein the CNS tissue is in tissue culture. Weiss teach the proliferation of neural and glial cell precursors in vitro and further teach culture of such cells from a patient from in vivo tissue to culture, see in particular columns 22-23.

New claims 63 and 64 recite intrastriatal administration via continuous infusion. Weiss teaches methods and compositions for the treatment of Parkinson's disease where new cells are generated in the striatum via administration of growth factors to the lateral ventricle or at the site of lesion, see in particular column 22, lines 10-18, column 26, lines 41-45 and column 60. Weiss also teaches where administration of the neural precursors/progeny may be administered at the lesion site, see in particular column 62, line 63- column 63, line 50. In addition, Weiss teach infusion into the lateral ventricles for six consecutive days and thus is via continuous infusion, absent further clarification of the requisite time period, see in particular column 28, lines 1-9, 18-26, 60-67 and Example 27.

Further as to the mechanism of action of such administration, Weiss teaches that the neural stem cell progeny can migrate into regions that have been damaged as a result of injury or disease, see in particular column 26, lines 10-12. Weiss further teaches that in vivo infusion results in the induction of proliferation migration and

differentiation of neural stem cells and progenitor cells in vivo, see in particular column 27, lines 20-24. Thus, the reference teachings anticipate the claimed invention.

Status of Claims

14. No claims are allowed.

15. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

16. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (703) 308-4242.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sharon L. Turner, Ph.D. whose telephone number is (703) 308-0056. The examiner can normally be reached on Monday-Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz, can be reached at (703) 308-4623.

Sharon L. Turner, Ph.D.
April 21, 2003

Gary L. Kunz

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